EXHIBIT 10

EXPERT REVIEWS

Meshology: a fast-growing field involving mesh and/or tape removal procedures and their outcomes

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Stress urinary incontinence and pelvic organ prolapse are two of the commonest conditions affecting women today. It is associated with significant compromise to quality of life. Through the years, there has been an evolution of technique and graft material to augment repairs for durability. Transvaginal placements of synthetic mid-urethral slings and vaginal meshes have largely superseded traditional tissue repairs in the current era because of presumed efficacy and ease of implant with device 'kits'. The use of synthetic material has generated novel complications, including mesh extrusion, pelvic and vaginal pain and mesh contraction. In this review, our aim is to discuss the management and outcomes associated with mesh removal. In addition, we will briefly review the safety communications issued by the US FDA on transvaginal mesh placement and a new classification system for complications arising from the use of synthetic graft endorsed by both the International Continence Society and International Urogynecological Association.

Keywords: complications • US FDA • mid-urethral slings • outcomes • pelvic organ prolapse • stress urinary incontinence • vaginal mesh

Utilization of graft in pelvic floor reconstruction has been around for more than a century. In reconstructive surgery, this can be generally classified into biologics (autologous, allografts or xenografts) or synthetic (absorbable or non-absorbable). In the beginning, various autologous tissues were harvested to augment repairs for incontinence and vaginal prolapse often with significant associated morbidity. The tide turned when general surgeons began using synthetic mesh for inguinal hernia repairs with reported outcomes that were vastly superior and more durable as compared with native tissue repairs [1]. It was only a matter of time before this expanded into use for pelvic floor conditions. However, the functional requirements of the vagina for optimal urinary, defecatory and sexual functions extends well beyond being durable and is vastly different from that of an abdominal or hernia repair. In 1994, Amid classified synthetic grafts as type 1 to IV depending on the pore size (macro >75 mm, micro <75 mm) and filamentous (monofilament and multifilament) nature of the material [2]. Type 1 meshes are preferred for their macroporous and monofilament nature, as it is associated with the lowest risk of infection while allowing for passage of macrophages and in growth of fibroblast and collagen. Early experiences with type II and type III synthetic meshes in pubovaginal sling and prolapse surgery were associated with significant mesh complications, which led to general abandonment of synthetic material use in pelvic reconstructive surgery. Erosion rates of 20–30% were reported in patients after implantation of Dacron, Mersilene and PTFE mesh materials and this may be attributable to their woven, multifilamentous and/or microporous nature limiting host-tissue in growth and promoting bacterial replication, leading to erosions, draining sinuses and fistulae [3,4].

A multitude of surgical procedures have been described and modified in hope of attaining a durable cure for stress urinary incontinence (SUI) and pelvic organ prolapse (POP). These surgeries were traditionally performed using the patient's native tissues. In an effort

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to decrease morbidity, improve surgical outcomes and minimize the complexity of some of these operations, an increasing number of repairs using synthetic mesh and biomaterials from cadaveric or xenograft tissues have been employed. Although similar meshes are used to treat SUI and vaginal prolapse, they remain for all intents and purposes two separate clinical entities with differing complications and outcomes from explantation surgeries and should be regarded as thus.

The introduction of tension-free vaginal tape (TVT) mid-urethral synthetic (MUS) sling in 1998 was a game changer for pelvic reconstructive surgeons in many ways [5]. Not only did it become the current gold standard for treatment of SUI, but it also paved the way for the US FDA approval with the 501K process for transvaginal mesh prolapse repair [6]. Not surprisingly, encouraged by the success of the MUS slings, transvaginal mesh and various 'kits' were promoted extensively [7]. For a moment, it looked promising when superior anatomical outcomes were reported in a few short-term studies [8,9]. However, complications started to emerge in what in retrospect was probable inadequate scientific rigueur to support their wide use; and reports of mesh erosions, pain and contractions surfaced, presenting often at times beyond the duration of the trial protocols [10]. The FDA intervened [11,12], and as it stands many specialty practices dealing with Female Pelvic Medicine and Reconstructive Surgery (FPMRS) have entered the dominion of what we term 'meshology', an evolving field of sub-specialization dedicated to a growing population of affected women with complications from synthetic materials (Supplementary Appendix 1 [supplementary material can be found online at www.informahealthcare.com/suppl/10.1586/17434440.2015.985655]).

This review aims to provide an overview of complications associated with the surgical treatment of SUI and POP related to synthetic material and the treatment outcomes associated with revision surgeries. We will also review the new International Urogynecologic Association (IUGA)/International Continence Society (ICS) classification of complications for insertion of prosthesis or grafts in female pelvic floor surgery and the recent FDA notifications [11–13].

Mesh in SUI

Synthetic material has been used in the treatment of SUI with a wide variety of retropubic MUS, transobturator (TOT) MUS and single incision mini-slings. In 2007 and 2009, approximately 95,000 synthetic slings were placed in the USA and 39,000 in France for SUI, respectively [14,15]. Success rates were estimated at 51–99% for retropubic and TOT slings [16–18]. Single incision mini-slings have demonstrated lower success rates so far, ranging from 31 to 92% [19,20]. Although extremely low rates of bowel injury, vascular injuries and death have been reported in the literature with the retropubic MUS, some surgeons prefer to use TOT MUS to avoid these devastating complications and reduce the fairly common risk of bladder injury [10,21,22]. Similarly, the mini-sling was devised as a less invasive procedure that could be performed safely in an office setting.

Despite these technological advancements, placement of synthetic material for SUI treatment may result in both minor and serious complications. Lower urinary tract symptoms may be exacerbated with worsened or *de novo* urgency and urge incontinence in 11–28% [23,24]. MUS placement focuses on tension-free positioning but ways of achieving a tension-free placement is not standardized and difficult to assess intra-operatively [25]. Furthermore, the emphasis on single incision slings is the reverse, with greater tensioning for greater compression of the urethra. Daneshgari *et al.* reviewed the complication rates of MUS in published data between 1995 and 2007 and reported complication rates that ranged from 4.3 to 75.1% for retropubic and 10.5 to 31.3% for TOT MUS. Retropubic approach had a higher occurrence of complications such as bladder perforation and hematoma. Groin pain was more common after the TOT approach [26].

Bladder outlet obstruction (BOO) and/or voiding dysfunction can result from tension at time of sling placement but also from tissue contraction and fibrosis in response to secondary scarring. MUS complications with vaginal extrusion or exposure maybe attributed to surgical technique but also vaginal atrophy, with related symptoms of vaginal bleeding, vaginal discharge or pain with intercourse for the patient or their partner (hispareunia) [27]. Erosion into the urinary tract most commonly involve the bladder and/or urethra presenting with urinary frequency, urgency, dysuria, recurrent urinary tract infections or calculi. Although persistent groin and medial thigh pain have been reported following TOT MUS, transient pain is fortunately more common occurring in 5–31% [28–31]. Pelvic pain and dyspareunia have been reported in up to 24% following MUS, and can be a most distressing and potentially irreversible complication to treat [32,33].

Evaluation of patients with MUS-related complications

As the long-term consequences of MUS are still unknown, patients with MUS placed for SUI should continue to undergo long-term follow-up to monitor for delayed symptoms or complications [34–36]. Complications with MUS can occur several years later and the field is becoming increasingly litigious [37]. As emphasized by the FDA notifications, women after MUS placement who do not have complications should not undergo explantation [34]. A detailed history should screen for vaginal discharge, vaginal bleeding, pelvic or groin pain, dyspareunia, hispareunia, urinary tract infections, urinary urgency, incomplete emptying, prolonged or slow urinary stream as well as bowel complaints. Onset of the symptoms, type of MUS used preferably based on an operative report, prior pelvic surgeries, investigations and treatments should be recorded. A pelvic exam is necessary to assess for vaginal exposure, prominence of scar tissue, recurrence of SUI and areas of tenderness or discomfort. In women unable to tolerate the exam, an examination under anesthesia may be required. Urethro-cystoscopy can be useful to identify MUS exposed in the lower urinary tract (Figure 1A–C) and distortion of the urethral lumen (Figure 2A). For voiding complaints, urodynamic

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studies and voiding cystourethrogram (VCUG) with lateral views have been useful. For bladder outlet obstruction following MUS placement, patients may demonstrate detrusor overactivity but more consistently will exhibit a prolonged or intermittent flow curve with an elevated detrusor pressure on urodynamic testing (Figure 2B). Another finding of bladder obstruction secondary to MUS on VCUG is urethral narrowing and kinking at the level of the MUS with proximal urethral dilatation (Figure 2C) [38]. Present imaging strategies with pelvic MRI and translabial ultrasound are generally of limited use for presurgical planning, but sometimes identify the course of the tape, especially after a prior limited procedure has been done such as office 'trimming' or incision.

Figure 1. Mesh erosion with stone formation. (A) Cystoscopic view of mesh extended at the right side of the bladder neck, covered with calcifications 5 years after placement of a retropubic midurethral sling. **(B)** Holmium laser (365 micron fiber) was used to eliminate as many mesh fragments as possible. **(C)** Cystoscopic view of completed laser resection of the bladder neck mesh revealing no residual tape.

Management & outcomes

There is a knowledge gap in treatment outcomes related to management of MUS complications. The majority of studies published are either case reports or small series from single centers with short duration of follow-up. Short case series have addressed the management of women with specific symptoms after MUS placement such as chronic pelvic pain, voiding dysfunction, dyspareunia/sexual dysfunction, urogenital fistulas and vaginal mesh extrusion or erosion into the lower urinary tract [32,33,39,40]. Table 1 summarizes the majority of published literature with functional outcomes relating to MUS removal or lysis [41–54]. Although most of the series are from tertiary referral centers, the pervading message is that the rate of these removal procedures is on the rise. This observation prompted the implementation of a universally accepted classification system for tape and mesh complications, which will be reviewed later on.

In some women, either complete or partial removal of the MUS is the only effective treatment modality. MUS removal can be performed transvaginally, retropubically or less frequently during a combined abdominal-vaginal approach. MUS removal is challenging as visualization is often limited and the extent of tissue damage from the MUS is often unknown. The risks of bleeding, incomplete removal, urethral injury, secondary urethro-vaginal fistula or urethral stricture have been reported, thus prompting some patients to attend tertiary referral centers for these removal procedures [55]. A tape excision technique is depicted in Figure 3A–C [56]. Beyond the immediate intra-operative risks lays ahead the concern for secondary urinary incontinence and its management. Baseline incontinence severity is often biased by patient recollection, and prolonged changes in the urethral wall from the MUS can have unpredictable outcomes in terms of potentially permanent sphincteric

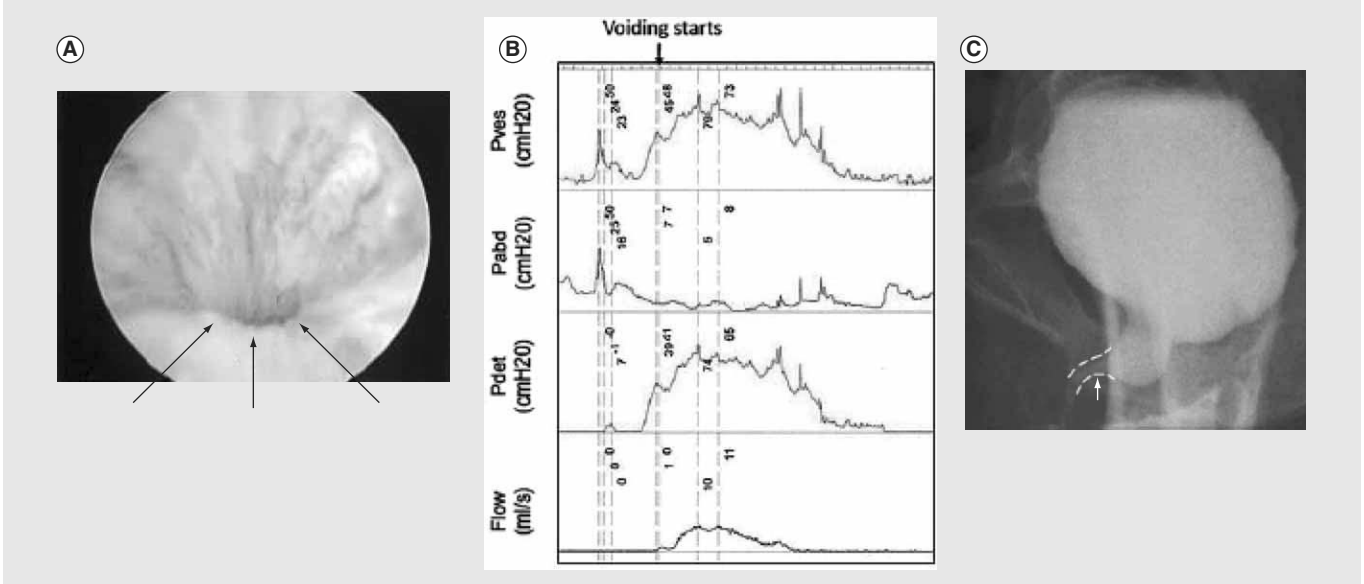

Figure 2. Diagnosis of urethral obstruction. (A) Cystoscopy revealed no exposed tape but a very narrow lumen with elevation and flattening of urethral floor depicted by the arrow. **(B)** Urodynamics and voiding cystogram. **(C)** Confirmed obstruction and its site (arrow on 2C).

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Table 1. Outcomes following mid-urethral sling excision.

Study (year)	Symptoms	Patients (n)	Intervention	Mean follow-up (months)	Outcomes (improbed or cured)/(%)	Ref.
Hammett *et al.* (2014)	Chronic pain	22	Sling excision	1.5	95	[41]
	Dyspareunia/hispareunia				42	
	Urinary retention				100	
	Urge incontinence				100	
Agnew *et al.* (2014)	Mesh exposure/extrusion	47	Sling excision	NR	100	[42]
	Vaginal/pelvic pain				100	
	Mesh infection				100	
Hou *et al.* (2014)	Chronic pain	55	Sling excision	35	81	[43]
Tijdink *et al.* (2011)	Mesh extrusion	15	Sling excision	6	92	[44]
	Pelvic pain					
Misrai *et al.* (2009)	Mesh extrusion	75	Sling excision	38.4	100	[45]
	Mesh erosion		Transvaginal removal		100	
	Urinary retention				82	
	Chronic pain				100	
Klutke *et al.* (2001)	Urinary retention/BOO	17	Sling release	13	100	[46]
South *et al.* (2009)	Urinary retention/BOO	30	Sling release	43–49	84	[47]
Ordorica *et al.* (2008)	Urinary retention/BOO	25	Sling excision/urethrolysis	NR	60	[48]
	Vaginal/bladder extrusion		Transvaginal/transvesical removal		100	
Nguyen (2005)	Urinary retention/voiding dysfunction	10	Sling loosening	12	100	[49]
Price *et al.* (2009)	Voiding dysfunction	33	Sling loosening/incision	3	100	[50]
Laurakinen and Kiilholma (2004)	Urinary retention	48	Sling incision/resection	N/A	88	[51]
Gamé *et al.* (2006)	Urinary retention	30	Sling incision	26	70	[52]
Kasturi *et al.* (2011)	Voiding dysfunction	15	Sling incision	6	100	[53]
Agnew *et al.* (2012)	Voiding dysfunction	63	Sling incision/excision	N/A	87	[54]

BOO: Bladder out let obstruction; N/A: Not available; NR: Not reported.

damage and/or bladder wall changes. Therefore, the management of urinary incontinence after MUS removal can be very challenging in women who have already undergone at least two procedures (MUS and MUS removal) and may be hesitant to pursue additional repairs even using their native tissues.

Voiding dysfunction

A major concern after an anti-incontinence surgery is outflow obstruction. There is no known technique that can control for the amount of tension exerted on the urethra no matter how loose the sling is placed. Even the TVT can later on retract, travel deep in the wall of the urethra and end up causing obstruction despite what appeared to be a perfect intra-operative placement based on the operative note. Raised voiding pressures due to obstructive changes have been consistently reported after any type of sling surgical procedures. With MUS, the recent TOMUS trial reported a greater proportion of obstructive urodynamic changes in the retropubic slings compared with the TOT MUS group [21]. A recent review on MUS complications by Stanford and Paraiso reported voiding dysfunction (16.3%), detrusor overactivity (15.4%) and urinary retention (14.2%), respectively [57]. Voiding dysfunction rates are estimated between 2.8 and 38% following a retropubic sling, and 0 and 15.6% with the TOT approach [53]. Fortunately, persistent post-operative voiding dysfunction requiring surgery following MUS placement is relatively rare. Population

studies have estimated the risk of sling revision/removal for either MUS erosion or retention to being fairly low, ranging from approximately 1 to 3% and 0.6 to 1.2% [22,23], respectively. Jonsson-Funk-*et al.* reported a 9-year cumulative risk of sling revision/removal at 3.7% (95% CI: 3.5, 3.9) in a large cohort of women sampled from a commercially insured database. The risk appears greatest at 1 year 2.2% and increased to 3.2% at 4 years before plateauing, with 60% of revisions/removals due to MUS erosion. Predictors for sling revision/removal included younger age with the higher risks among those aged 18–29 and also among women who had a concomitant anterior or apical prolapse procedure [58].

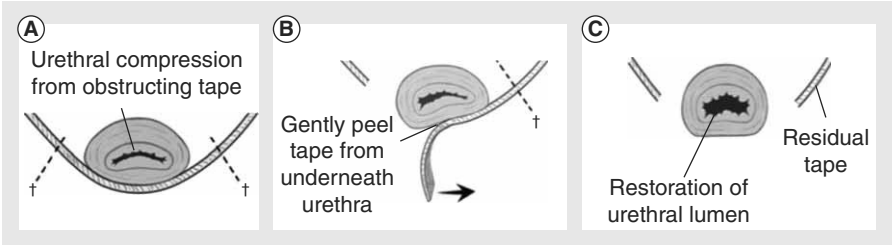

Figure 3. Sling removal technique. (A) Midurethral synthetic placed underneath the urethra should be tension free but can result in urethral kinking and distortion. It is preferable to incise the tape on the side of the urethra (marked by†) to reduce risk of urethral injury. **(B)** Tape is carefully peeled away from underneath the urethra. **(C)** After midurethral tape excision, urethroscopy helps confirm no urethral injury and documents restoration of a normal urethral lumen.

For urinary retention following placement of a MUS that persists for >1 week, loosening the sling or sling incision is recommended. Despite a prior sling incision at another institution, we caution the reader about some patients who continue to have obstructive symptoms and clinical evidence of obstruction on urodynamics and VCUG, and may ultimately require excision of the tape and/or urethrolysis. It is likely that the longer the obstruction remains untreated, prolonged compression and ischemia of the midurethra can result in permanent scarring of the urethral lumen and consequently voiding dysfunction and bladder remodeling [55,59]. Behavioral therapy and anticholinergics have been reported for *de novo* detrusor overactivity following sling placement. Urgency symptoms frequently occur as a result of BOO; and thus BOO should be excluded for any *de novo* symptoms after a sling procedure [60,61]. In this case, tape excision to relieve the obstruction would be necessary.

Sling division (in the midline or laterally) is generally performed these days. As seen in Table 1, the estimated success rate of improvement and/or resolution from this review ranges from 60 to 100%. Klutke *et al.* was one of the first to report on their series of sling mobilization and division of TVT for BOO with 100% resolution. The mean time to surgery from MUS placement was 64 days (range 6–228 days) and no women had recurrent stress incontinence [46]. There is conflicting evidence concerning the timing of sling release. South *et al.* compared subjects who had an early sling lysis (≤1 year from sling to lysis) to a late sling lysis (>1 year) in 112 women. There was an overall 84% improvement in LUTS after midline sling lysis with early group showing greater improvement over late sling lysis group (91 vs 71%; p = 0.01). On multivariate logistic regression model, which included age, prior urethrolysis, preoperative complete retention and type of sling, this finding retained statistical significance (odds ratio [OR]: 4.0; 95% CI: 1.2–13.2) [47]. Furthermore, there are data to suggest that delayed urethrolysis may be associated with persistent voiding dysfunction [59]. However, Agnew *et al.* reported the opposite with 6/45 (13%) of the early revision group and 2/18 (11%) of the late revision group experiencing persistent voiding dysfunction after revision [54].

Pelvic/vaginal pain/dyspareunia

The etiology of chronic pain after MUS surgery is multifactorial. A complex interplay of factors can be causative, including synthetic material type, nerve and muscle injury, infection, contraction, erosion or extrusion, and this is beyond the scope of this review [62]. At present, there is no consensus on management of persistent pain following MUS placement. Strategies include expectant management with physical therapy, pain medications, infiltration or even MUS removal. The incidence of chronic/persistent pain following MUS placement varies from 0 to 30%. Petri and Ashok reported on the management of 280 cases of late sling complications (RP 210 and TO 70). Compared with the retropubic MUS group, the TOT group had greater number of complications related to persistent pain (10% TVTs vs 32% TOT tapes), dyspareunia (3 vs 18%) and tape-related infections (4 vs 18%) [63]. Similarly, Latthe *et al.* in a meta-analysis evaluated 11 randomized controlled studies comparing the TOT approach (630 patients) versus the retropubic approach (633 patients) for the treatment of SUI. They reported a higher rate of pain in the TOT group (12%) than in the TVT group (1.3%) with an OR of 9.34 [64]. In this review, the estimated success rate based on current literature for treating pelvic pain with MUS removal varied from 95 to 100% [41–45]. In contrast to the management of voiding dysfunction where optimal outcomes could be achieved with MUS incision, MUS excision is preferred for the treatment of pain-related complications. Agnew *et al.* reported on 47 patients requiring MUS removal (with partial or complete excision) indicated for exposure/extrusion (83%) and pain (17%) with 100% success in both groups. Interestingly, one in five women in their study with complications presented more than 5 years after initial MUS insertion, emphasizing the need for long-term vigilance. One-third of their patients required additional anti-incontinence procedures for recurrent SUI [42]. Groin pain is a recognized complication of trocar-based system, which has been reported in up to 4% after TOT placement. Its course is usually transient, but can be intractable requiring extensive obturator dissection and MUS excision with variable success [65].

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Table 2. Outcomes of sexual function following sling surgery.

Study (year)	Complaints	Sling placed	Indication	Patients (n)	Intervention	Follow-up (mean)	Outcomes	Refs.
Kuhn *et al.* (2009)	Dyspareunia	TOT 10 RP 8	SUI	18	Sling excision	3	FSFI/VAS Improvement in all domains except orgasm Satisfaction; decreased	[69]
Kuhn *et al.* (2009)	Mesh extrusion	TOT 12 RP 9	SUI	21	Vaginal epithelial resuture	6	FSFI/VAS Improvement in all domains except orgasm Satisfaction; decreased	[70]

BOO: Bladder outlet obstruction; FSFI: Female sexual function index; LUTS: Lower urinary tract symptoms; RP: Retropubic; QoL: Quality of life; SUI: Stress urinary incontinence; TOT: Transobturator; UDI-6: Urogenital distress inventory; VAS: Visual analog scale.

Sexual dysfunction

Studies on female sexual dysfunction after MUS placement have been few, involving small size and cohort case studies. A significant issue is the underreporting of these complications in general. Dyspareunia and mesh extrusion following surgery is the commonest cause of sexual dissatisfaction [63,66,67], but orgasmic dysfunction has also been reported to play a role [67]. In addition, feelings of anxiety and distress from worrying about potential urinary leakage during sexual activity may not resolve once stress incontinence is treated. This, together with unrealistic patient expectations, may also explain the sexual dissatisfaction after MUS surgery in some women [68]. Table 2 summarizes the available studies on MUS complications related to female sexual function. Kuhn *et al.* reported on sexual and satisfaction outcomes using FSFI and visual analog scale (VAS) in a series of 18 women presenting with *de novo* dyspareunia after MUS (10 TOTs and 8 TVTs) treated with MUS excision. They noted improvement in FSFI scores in most domains except orgasm, which deteriorated. Interestingly, satisfaction rates deteriorated from a median of 7 (95% CI: 6.3–7.7) to a median of 4 (95% CI: 3.7–5.1), but this was not statistically significant ($p = 0.99$) [69]. In addition, the same authors reported further in a subpopulation of 21 women with MUS extrusion who were treated with topical estrogen in 3 and vaginal epithelial re-suturing in 18. There was consistent improvement in all domains of FSFI: desire ($p < 0.0001$), arousal ($p < 0.0003$), lubrication ($p < 0.0001$), satisfaction ($p < 0.01$) and pain ($p < 0.0001$) except orgasm, which remained unchanged ($p = 0.41$) [70].

Mid-urethral sling exposure/extrusion

Vaginal extrusion/exposure may be managed conservatively if exposure is <1 cm and not associated with any complicating factors [71,72]. Local estrogen therapy is often employed but the literature reflects mixed results [71,73]. If vaginal extrusion/exposure is larger or fails to heal satisfactorily with conservative measures, excision should be considered [71–74]. Often a limited excision is attempted under local anesthesia in cases of small persistent areas of vaginal exposure [73,74]. Management of MUS involving the urinary tract, termed extrusion, has been reported with excision via either the vaginal or abdominal approaches, or endoscopically with ablation with holmium laser or transurethral resection with electrocautery [75,76]. Combined laparoscopic and endoscopic procedures have also been described [77].

Mesh in POP

Much has been published on the use of synthetic vaginal mesh for the treatment of POP. Since the recent communications issued by the FDA, it has been placed under intense scrutiny and, to some extent, divided management opinions among pelvic floor reconstruction surgeons. The repercussions have also extended to the legal community, where class action lawsuits are in effect, pursuing the medical industry to be held accountable in regards to mesh safety.

Just how we arrived to our present circumstance deserves some mentioning. In an era where native tissue repairs were the first-line option, recurrences were of concern to pelvic floor surgeons. Similarly, the reporting of prolapse outcomes lacked standardization and were not inclusive of patient-reported outcome measures. Therefore, mesh repairs were introduced to reduce recurrence and improve durability. With the success of the TVT, vaginal mesh devices were cleared through the FDA 510 (k) process without additional post-marketing studies [78]. Many companies started to market mesh kits to simplify their placement transvaginally. However, a series of reports on 'unique' mesh-related complications (mesh extrusion, erosion and/or retraction, as well as pain and infection) emerged (Figure 4A & B).

Some of these complications were found to be irreversible and crippling, leading to two consecutive FDA notifications in 2008 and 2011. Data abstracted from a recent systematic review conducted by the Society of Obstetrics and Gynecology of Canada in 2010 reported that although mesh repairs had an anatomical success rate of 79–100%, mesh erosion rate was 5–19% and reoperation rate was 3.2–22% [79]. These numbers, derived from high volume and experienced centers, have implications for less experienced pelvic surgeons, although caseload and experience levels have not been officially quantitated to date.

Similarly, a recent systematic review of the incidence and management of vaginal mesh repair-related complications with graft material (synthetic and biologic) from the Society of Gynecologic Surgeons reported on an overall erosion rate of 10.3% (95% CI: 9.7–10.9%; range: 0–29.7%; synthetic: 10.3%; biological: 10.1%) from meta-analyzed data in 110 studies. Dyspareunia was reported in 70 studies with a rate of 9.1% (95% CI: 8.2–10.0%; range: 0–66.7%; synthetic: 8.9%; biological: 9.6%). Interestingly, overall erosion rates between synthetic and biological grafts were similar, although they widely varied across studies. Management differed as most biological graft erosions were managed conservatively, while synthetic graft erosions often required operative revision. Most erosion events occurred within 12 months of implantation and typically presented with vaginal discharge, vaginal pain and/or dyspareunia. Advancing age and concomitant hysterectomy were the most common predisposing factors for mesh erosion [80].

Due to alarming reports of litigation concerning vaginal mesh adverse events, outcomes of native tissue repairs have been re-examined. As a result, re-evaluation of prior published studies with modified criteria for failure has led to a change in the rate of anatomic recurrence noted after native tissue cystocele repairs. The original data of a landmark randomized controlled trial by Weber and collaborators, describing a low anatomical success (30–46%) with native repair, was reanalyzed using more clinically relevant definitions of success based on the NICHD Pelvic Floor Disorders Network's recommendation. Of the 114 subjects randomized to the three treatment arms, 88% were successful based on the new definitions with no difference between the three groups. No reoperations were reported for complications or recurrence at 12 months [81]. A study by Barber *et al.* using the Colpopexy and Urinary Reduction Efforts trial data re-evaluated their outcomes based on 18 definitions of surgical success. Treatment success varied widely depending on definitions used (19.2–97.2%). Definition of surgical success correlated most with both treatment success and overall improvement when the following was utilized: absence of prolapse beyond the hymen (94%), absence of bulge (92.1%) and absence of re-treatment (97.2%). Importantly, subjective cure was associated with significant improvements in the patient's assessment of both treatment success and overall improvement, more so than any other definition considered ($p < 0.001$ and $p < 0.001$, respectively) [82].

Moving forward, the Austrian Urogynecology Working Group initiated a transvaginal mesh registry and examined peri-operative data, as well as outcomes at 3 and 12 months (726 transvaginal procedures with 10 different transvaginal kits). The reported mesh exposure rate was 11% at 3 months and 12% at 12 months. *De novo* bladder symptoms were reported in 39 (10 %) at 3 months and in 26 (11 %) at 12 months. Dyspareunia was reported at 7 and 10% of 265 and 181 sexually active patients at 3 and 12 months postoperatively, respectively. These figures were comparable with established reported series [83].

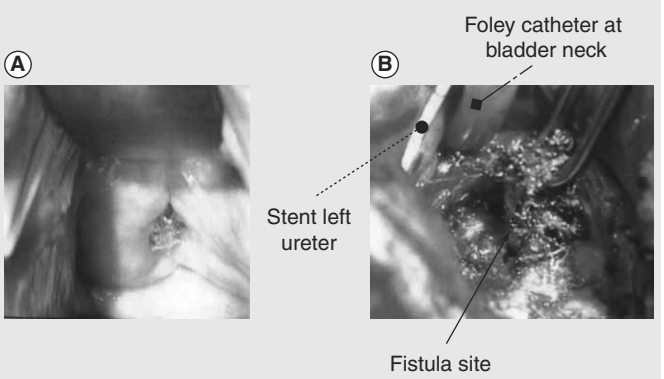

Figure 4. Vaginal mesh extrusion. (A) Anterior vaginal midline mesh erosion and an associated vesicovaginal fistula. Site of mesh erosion was located near the left ureteric orifice by cystoscopy. **(B)** Surgical options for vesicovaginal fistula involving an exposed mesh include transabdominal or transvaginal repairs. Transabdominal repair of the vesicovaginal fistula with removal of mesh was performed. The left ureteric orifice was in very close proximity to the fistula and is depicted by the arrow, but was not reimplanted.

Management & outcomes

Although the spectrum of complications relating to transvaginal mesh placement is well documented in the published literature [84], the opposite can be said about surgical outcomes following treatment of these complications. There is a paucity of data from surgical removal of transvaginal mesh with adequate follow-up duration to guide physicians when managing these potentially complex patients. Table 3 summarizes the available studies on mesh excision [41,43,85–92].

Mesh erosion

A recent randomized controlled trial reported by Sokol *et al.*, which randomized women with stage ≥2 prolapse to synthetic versus native repair, had to be halted as there was a 15.6% mesh erosion rate with higher reoperation rate. At 12 months, both groups had improvement in POP-Q points, with primary end point being prolapse stage ≤1. The measures to improve quality of did not differ between groups: 96.2% mesh versus 90.9% non-mesh subjects [93].

Data from meta-analysis by Abed *et al.* reported in 14 studies potential risk factors for graft erosion. The most commonly reported potential risk factor was concomitant hysterectomy, but other considered risk factors included patient age, surgeon experience, use of inverted 'T' colpotomy

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Table 3. Outcomes following mesh excision for prolapse.

Study (year)	Symptoms	Patients (n)	Intervention	Mean follow-up (months)	Outcomes (improved or cured)/(%)	Ref.
Danford *et al.* (2014)	Pelvic pain	233	Mesh excision/revision	NR	73	[85]
Hou *et al.* (2014)	Pelvic pain	69	Mesh excision	22	67	[43]
Crosby *et al.* (2014)	Mesh extrusion	84	Mesh excision	4	95	[86]
	Pelvic pain				84	
	Dyspareunia				84	
Hammett *et al.* (2013)	Mesh extrusion	23	Mesh excision	1.5	100	[41]
	Pelvic pain				95	
Lee *et al.* (2013)	Mesh extrusion	58	Mesh excision	13.3	100	[87]
	Pelvic pain				86	
Tijdink *et al.* (2011)	Mesh extrusion	48	Mesh excision	6	92	[88]
	Pelvic pain					
Feiner and Maher (2010)	Pelvic pain	17	Mesh excision	6	88	[89]
	Dyspareunia				64	
Ridgeway *et al.* (2008)	Mesh exposure	15	Mesh excision	8.3	87	[90]
	Pelvic pain				87	
	Vesicovaginal fistula				100	
Hurtado and Appell (2009)	Mesh exposure	12	Mesh excision	3.4	100	[91]
	Pelvic pain				50	
Skala *et al.* (2011)	Mesh extrusion	48	Mesh excision	3	100	[92]
	Pelvic pain				46	

NR: Not reported.

incisions, smoking and diabetes mellitus. Graft erosion symptoms included vaginal discharge, vaginal pain, dyspareunia or pain experienced by the sexual partner. A total of 76 studies reported on management of graft erosions with synthetic mesh involving 795 women: 165 (21%; pooled, not meta-analyzed, estimate) were successfully treated with estrogen or antiseptic agents, 87 (11%) were successfully treated with excision in the surgeon's office and 448 (56%) were treated with surgical excision in the operating room, with some women requiring two to three additional surgeries to resolve symptoms [80]. Table 4 highlights high cure rate from mesh excision ranging from 92 to 100%. Complications following removal of transvaginal mesh are related to the affected compartment. For apical and anterior meshes, bladder and ureteric injury are of particular concern. For mesh complications involving the posterior compartment, bowel injury and need for colostomy have been reported [71]. Other complications associated with mesh excision include large vaginal defects, possibly requiring skin grafting; residual pain, which can be unremitting and life altering and/or need for repeat surgery.

Chronic pelvic & vaginal pain

Pain following pelvic floor reconstruction surgery is inherent to both native tissue and mesh prolapse repairs. Anterior colporrhaphy has an estimated 5–9% risk of dyspareunia [90]. However, new forms of pain syndromes have surfaced since the advent of 'mesh kits' with synthetic arm extensions into the ischiorectal fossa, transoburator foramen and sacrospinous ligament for prolapse repair. *De novo* dyspareunia rate of up to 38% has been reported following transvaginal mesh placement [94]. Withagen *et al.* studied the risk factors for mesh complications in 294 women treated with trocar-guided mesh kits for POP. They reported post-operative dyspareunia and *de novo* dyspareunia rate of 45 and 26%, respectively, and predictors for both were pre-existing pain pre-operatively [95]. Like the MUS, the mechanism leading to pain after mesh placement is likely multifactorial. A combination of nerve or muscle damage/entrapment and/or tension on vaginal or peri-vaginal structures as a result of retraction and scarring seem probable. Feiner and Maher defined a series of 'mesh contraction' in 17 women surgically managed with mesh excision. All subjects presented with intractable pelvic pain, dyspareunia and

Table 4. Pre- and post-operative mesh safety questions issued by FDA.

Before surgery	Are you planning to use mesh in my surgery? Why do you think I am a good candidate for surgical mesh? Why is surgical mesh being chosen for my repair? What are the alternatives to transvaginal surgical mesh repair for pelvic organ prolapse, including non-surgical options? What are the pros and cons of mesh in my particular case? How likely is it that my repair could be successfully performed without surgical mesh? Will my partner be able to feel surgical mesh during sexual intercourse? What if the surgical mesh erodes through my vaginal wall? If surgical mesh is to be used, how often have you implanted this particular product? What results have your other patients had with this product? What can I expect to feel after surgery and for how long? Which specific side effects should I report to you after surgery? What if the mesh surgery doesn't correct my problem? If I develop a complication, will you treat it or will I be referred to a specialist experienced with surgical mesh complications? If I have a complication related to the mesh, how likely is it that the surgical mesh could be removed and what could be the consequences? If a surgical mesh is to be used, is there patient information that comes with the product, and can I have a copy?
After surgery	Continue routine follow-up care. Notify healthcare provider if complications or symptoms: Persistent vaginal bleeding or discharge Pelvic or groin pain Pain with sex Let healthcare provider know if she has surgical mesh, especially if planning to have another related surgery or other medical procedures Talk to healthcare providers about any questions or concerns Ask the surgeon at her next check-up if she received mesh for pelvic organ prolapse surgery if she does not know if mesh was used

Modified from: US FDA, Urogynecologic Surgical Mesh: Update on the Safety and Effectiveness of Transvaginal Placement for Pelvic Organ Prolapse, July 2011. Important questions patient should address with the surgeon pre-operatively according to the FDA Safety Communication Update (12 July 2011) are included in this table. A summary of basic aspects of care following mesh surgery is included for the patient.

tenderness on pelvic examination associated with vaginal scarring. Improvement post-operatively was pelvic pain (88%) and dypareunia (64%), respectively, with 12% reporting residual bothersome symptoms [89].

Skala *et al.* reported an overall cure rate of 46.3% (25 women) at 3 months following surgical mesh excision in 54 women with transvaginal mesh kit complications. Of these women, 11 required additional revision surgery and the overall transvaginal versus laparotomy approach to mesh excision was 77 and 23%, respectively. Post-treatment, persistent dyspareunia was 36% [92]. Similarly, Tijdink *et al.* evaluated 73 women with mesh excision for mesh-related complications retrospectively. The primary complaint was pain (77%) and mesh erosion (76%); 56% of women had mesh for greater than 2 years prior to excision surgery. Surgical excision was beneficial in 92% of cases with symptomatic improvement and recurrent POP was 12% mostly affecting the anterior compartment [88].

FDA notifications

In October 2008, the FDA released a Public Health Notification in response to complications associated with urogynecologic use of surgical mesh [11]. In July 2011, based on the Manufacturer's and User Device Experience (MAUDE) database, the FDA conducted a search of the adverse events reporting 3979 cases from January 2005 to December 2010, with a fivefold increase in reports of adverse events in POP repairs from January 2008 to December 2010. An 'Update on the Serious Complications Associated with Transvaginal Placement of Surgical Mesh for POP' was issued [12]. Unlike the 2008 notification, the 2011 FDA Safety Communication stated that complications 'are NOT rare' and that 'transvaginally placed mesh in POP repairs does NOT conclusively improve clinical outcomes over traditional non-mesh repairs'. The Safety Communication aimed to educate the public and healthcare providers with adverse events relating to these devices and provided recommendations for informed decision-making regarding transvaginal mesh. In September 2011, an advisory panel of experts assembled for an open public hearing and presentations by both industry and the FDA to address questions regarding mesh safety for urogynecological applications for POP and SUI. Regarding transvaginal placement of mesh, the advisory panel reached a number of consensus including the following: the safety, efficacy and benefit ratio is not well established in transvaginal mesh, improved premarket studies comparing mesh to non-mesh options need at least 1 year follow-up, transvaginal meshes should be reclassified to Class III, post-market studies need to be ongoing and mesh for abdominal sacrocolpopexy would not require reclassification. Patients were

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Table 5. Terminology involved in the classification of complications related directly to insertion of prosthesis (meshes, implants, tapes) or grafts in female pelvic floor surgery.

Definitions	
Prosthesis	A fabricated substitute to assist a damaged body part or to augment or stabilize a hypoplastic structure
Mesh	A (prosthetic) network of fabric or structure
Implant	A surgically inserted or embedded prosthesis
Tape (sling)	A flat strip of synthetic material
Graft	Any tissue or organ for transplantation. This term will refer to biological materials inserted
Autologous grafts	From the woman's own tissues (e.g., dura mater, rectus sheath or fascia lata)
Allografts	From post-mortem tissue banks
Xenografts	From other species (e.g., modified porcine dermis, porcine small intestine, bovine pericardium)
Complication	A morbid process or event that occurs during the course of a surgery that is not an essential part of that surgery
Contraction	Shrinkage or reduction of size
Prominence	Parts that protrude beyond the surface (e.g., due to wrinkling or folding with no epithelial separation)
Separation	Physically disconnected (e.g., vaginal epithelium)
Exposure	A condition of displaying, revealing, exhibiting or making accessible (e.g., vaginal mesh visualized through separated vaginal epithelium)
Extrusion	Passage gradually out of a body structure or tissue
Compromise	Bring into danger
Perforation	Abnormal opening into a hollow organ or viscus
Dehiscence	A bursting open or gaping along natural or sutured line

Adapted from [13].

encouraged to ask their surgeons several pertinent questions before proceeding with mesh placement [12] (Table 4). The advisory panel felt that the safety and efficacy of retropubic and TOT MUS is established, whereas single-incision mini-slings require further investigation and should be used in study setting with long-term follow-up. More recently, many companies like Johnson & Johnson have withdrawn some of their mesh products from the market [96], while other continue to offer products such as Elevate™ by AMS®.

Although it is recommended that mesh and device complications are reported to the FDA through its MedWatch, the FDA Safety Information and Adverse Event Reporting program or respective national equivalent (MAUDE), surgeons and clinicians underreport adverse events as the reporting process can be time consuming and is completely voluntary [12]. Many acknowledge the need for a comprehensive registry of mesh use and outcomes [97,98]. Until such a national registry exists, recognition of device-associated complications will be further delayed until reported in the literature, thus exposing even more patients to these risks [98].

Fortunately, a national registry of outcomes of mesh in incontinence and prolapse is underway in both Australia and the UK, initiated by their national urogynecological societies [99]. The Urogynaecological Society of Australia database encourages its members to report their outcomes by offering the database at a low annual cost, giving CME credits for participating and arguing for the greater good since accurate surgical data will better support clinical and regulatory decisions. Companies marketing mesh products should be encouraged to employ code numbers and tracking systems to make identification and follow-up of mesh easier. Ideally, all mesh should be blue-colored to aid in removal when indicated. Transparent meshes are very difficult to identify when buried inside scar tissue. Special mesh design for recognition by MRI would be very desirable as it is difficult to know how much of the original mesh material is remaining after attempted excision and where it is located.

Classification of mesh complications

A classification system of complications related directly to the insertion of prosthesis in female pelvic floor surgery has been instituted by both the IUGA and ICS in efforts to standardize terminology for more precise reporting of complications and to facilitate the implementation of a reliable registry [13,98] (Table 5 for a list of the terminology). The classification system coding is based on category of complication, time of clinical diagnosis and site of complication. Pain is subclassified into five grades ranging from ***a*** (asymptomatic/no pain) to ***e*** (spontaneous pain). Although a patient may suffer different complications at different times, all complications should be listed with the final

Table 6. International Urogynecologic Association/International Continence Society classification of complications related directly to insertion of prosthesis (meshes, implants, tapes) or grafts in female pelvic floor surgery.

General description	A (asymptomatic)	B (symptomatic)	C (infection)	D (abscess)
1. Vaginal: No epithelial separation Include prominence (e.g., due to wrinkling or folding), mesh fiber palpation or contraction (shrinkage)	1A: Abnormal prosthesis or graft finding on clinical exam	1B: Symptomatic, e.g., unusual discomfort/pain; dyspareunia (either partner); bleeding	1C: Infection (suspected or actual)	1D: Abscess
2. Vaginal: Smaller <1 cm exposure	2A: Asymptomatic	2B: Symptomatic	2C: Infection	2D: Abscess
3. Vaginal: Larger >1 cm exposure, or any extrusion	3A: Asymptomatic 1–3A(a) if no prosthesis or graft-related pain	3B: Symptomatic 1–3B(b–e) if prosthesis or graft-related pain	3C: Infection 1–3C(b–e) if prosthesis or graft-related pain	3D: Abscess 1–3D(b–e) if prosthesis or graft-related pain
4. Urinary tract: Compromise or perforation including prosthesis (graft) perforation, fistula and calculus	4A: Small intra-operative defect, e.g., bladder perforation	4B: Other lower urinary tract complication or urinary retention	4C: Ureteric or upper urinary tract complication	
5. Rectal or bowel: Compromise or perforation including prosthesis (graft) perforation and fistula	5A: Small intra-operative defect (rectal or bowel)	5B: Rectal injury or compromise	5C: Small or large bowel injury or compromise	5D: Abscess
6. Skin and/or musculoskeletal: complications including discharge, pain, lump or sinus tract formation	6A: Asymptomatic, abnormal finding on clinical exam	6B: Symptomatic, e.g., discharge, pain or lump	6C: Infection, e.g., sinus tract formation	6D: Abscess
7. Patient: compromise including hematoma or systemic compromise	7A: Bleeding complication including hematoma	7B: Major degrees of resuscitation or intensive care	7C: Mortality (additional complication-no site applicable – S0)	
Time (clinically diagnosed)				
T1: Intra-operative 48 h	T2: 48 h–2 months	T3: 2–12 months	T4: over 12 months	
Site				
S1: Vaginal: area of suture line	S2: Vaginal: away from area of suture line	S3: Trocar passage Exception: intra-abdominal (S5)	S4: Other skin or musculoskeletal site	S5: Intra-abdominal
Grades of pain: subclassification of complication category				
Asymptomatic or no pain Provoked pain only (during vaginal examination) Pain during sexual intercourse Pain during physical activities Spontaneous pain				

Adapted from [13].

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category for a single complication reported at its maximal score (Table 6 for classification).

These complications emphasize the need for more deliberate and careful consideration by both the patient and the surgeon prior to surgery, with full informed consent outlining potential material risks [97]. The literature reporting mesh complications is mostly retrospective. As surgeons, we are unable to predict who will suffer an adverse event. It is unclear whether the contributing factors of these devastating complications result from poor surgical technique, deficient training, infection, patient factors or an inherent defect of the synthetic material. Marketing strategy rather than evidence-based data resulted in rapid adoption of mesh for POP [55,100]. In retrospect, surgical expertise with specialized training in proper patient selection, mesh insertion and management of associated complications is now advocated through credentialing processes [12,34,98]. Tightening FDA approval with more rigorous safety and efficacy testing for the licensing of new FPMRS-related surgical devices will be necessary to improve patient safety and trust [12,34,73,100]. There are still many unanswered questions in understanding vaginal tissue, the aging process and how exactly mesh placement affects the vaginal wall healing and inflammatory responses [55]. We also need to better understand mesh properties and biomechanics to ultimately create a more biologically compatible material to avoid potentially devastating and permanent complications.

What is evident within all these studies is the lack of objectivity in regards to reporting of functional outcomes following revision surgeries. At present, there is no established standard or benchmark to gauge our successes, and the original condition of the patient is often biased because of recollection. Just as there is now a new classification system endorsed by IUGA and ICS for reporting on prosthesis-related complications, the same should be considered for the development of an instrument that could categorically and objectively unify the reporting of outcomes associated with our revision surgeries. A clear objective for patient focused outcomes is a necessity as it should not only make published results more comparable, but it will also provide guidance on what to expect after a mesh revision. With increased vigilance, understanding and expertise in the field of meshology, it will be possible to achieve the best outcomes for our patients.

Conclusion

The notifications issued by the FDA surrounding transvaginal mesh placement have not only divided the community of pelvic floor reconstruction surgeons in POP management, but it has also triggered an alarming number of lawsuits against the manufacturers of the medical devices. Management of mesh complications in POP and SUI is now a rapidly growing field for surgeons, with explantation surgery emerging as an important new urological discipline. So much so that a new classification system for complications relating to prosthesis insertion has been endorsed by both the IUGA and ICS. There is an urgency to focus on basic research and reevaluate our treatment goals as we maybe entering into a state of 'clear and present danger'.

Expert commentary

The concept of utilizing mesh is based on decades of use in general surgery for hernia repair and abdominal sacrocolpopexy. As emphasized in the recent FDA notifications, there is no controversy on the use of robotic/laparoscopic/open approaches to place mesh to correct POP, especially when it is a recurrence or when several compartments are involved. However, there is a growing concern regarding the safety of transvaginal mesh placement as reported by the FDA. Further basic research is required in studying the properties of mesh (incorporation, retraction, long-term tissue reaction) as they interact with vaginal tissues, especially in younger individuals with a long lifetime risk. A challenging step now is to organize randomized controlled trials with adequately powered population samples and appropriate duration of follow-up to evaluate long-term outcomes. Although highly desirable for all implant surgeons to track their complication rates and outcomes related to revision surgeries, a mesh registry has not been implemented yet. Implanters need to provide full disclosure of personal experience and type of mesh material to be used to temper their exposure to the growing mass of litigations. Ultimately we need to honor the principle of primum non nocere' (first do no harm) to all our patients and be accountable for our actions.

Five-year view

We expect to see a return to basics with translational research thoroughly evaluating the characteristic of implanted vaginal mesh before clinical trials are initiated. A certification process for FPMRS should reinforce the qualifications and expertise of the implanters. Hopefully, large national registries and the FDA will continue to update on the status of current mesh safety as post-marketing study outcomes are disclosed. Non-synthetic mesh research will grow to design tissue-engineered repair materials. It is anticipated that a validated outcome instrument incorporating all essential life domains will be benchmarked in revision surgeries to standardize reporting.

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Key issues

- Management of mesh complications in the treatment of pelvic organ prolapse has become a rapidly growing field and should be dealt with by female pelvic medicine and reconstructive surgery specialists.
- As recommended by the US FDA, full disclosure of risks and benefits to the patient, as well as surgeon' s personal level of experience with a given mesh product is essential before consenting a patient for mesh surgery.
- An office-based outcome tool to uniformly report on the multidimensional outcomes associated with revision surgeries is required.
- Despite maximal mesh excision, chronic pelvic pain and/or dyspareunia may persist in a subset of women and be responsible for life-altering changes.
- Tightening of the FDA-approval process in the licensing of new transvaginal mesh surgical devices may have to be considered.
- Basic research will continue to evaluate the biomechanics properties of mesh with a focus on more biologically compatible materials.
- A National mesh registry should be established to provide adequate reporting of mesh/tape-related complications.

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